

Genetic basis of familial hypercholesterolaemia

A.C. Alves^{1,2}, M. Bourbon^{1,2}

1 Unidade de I&D, Grupo de Investigação Cardiovascular, Departamento de Promoção da Saúde e Doenças Crónicas, Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisboa, Portugal

2 Center for Biodiversity, Functional & Integrative Genomics (BioFIG)

Familial hypercholesterolemia (FH) is a genetic condition characterized by a high cholesterol concentration in the blood. The most frequent causes of FH are inherited defects in the Low Density Lipoprotein Receptor gene (LDLR) but, in a small percentage of patients, mutations in the apolipoprotein B gene (APOB) and in the proprotein convertase subtilisin/kexin type 9 gene (PCSK9) are also responsible for FH. These 3 genes are currently studied in the “Portuguese FH study”. From the 404 families with a clinical diagnosis of FH already studied only 48% of these have a mutation in one of the 3 studied genes, so other gene defects must exist to explain the cause of hypercholesterolemia in the remaining families.

The first aim was the exclusion of previously unidentified LDLR and APOB gene defects, as well as the exclusion of mutations in LDLRAP1 and CYP7A1 genes in patients with possible recessive hypercholesterolemia. A second aim was the whole sequencing of APOB gene, in 65 index patients without mutations in LDLR or PCSK9 genes or in fragments of exon 26 and 29 of APOB gene, by pyrosequencing, in order to identify the genetic cause of the hypercholesterolemia in these patients.

CYP7A1 and LDLRAP1 genes were analysed by PCR and direct sequencing. A pool of the 65 DNAs was sequenced by pyrosequencing method and a total of 227688 nucleotide reads were obtained, corresponding to a mean coverage of 35x/fragment/individual.

No mutations were found in LDLRAP1 and CYP7A1 genes in 10 patients with possible recessive hypercholesterolemia.

A total of 87 alterations were detected, being 27 described SNPs. From the 26 alterations detected, only 12 were found and 4 of these had not been previously described. After family studies only one alteration did not co-segregate in the family, providing further evidence that 3 of the alterations found can be mutations causing disease, but functional studies are required to prove pathogenicity.

Patients, in whom it was not possible to find the genetic cause of the hypercholesterolaemia, will continue to be studied, since all show a severe clinical phenotype of FH.